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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 01/20/04 CA

Office Action Summary	Application No.	Applicant(s)	
	09/986,632	AGUERA ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cov r sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *17-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *29 and 36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-16, 29 and 36) filed 12/22/2003 is acknowledged. Claims 1-43 are pending, with claims 17-43 withdrawn from consideration as being directed to nonelected inventions (*See infra*, Claim Objections, viz., claims 29 and 36).

Specification

Use of acronyms in both the claims and specification is improper, where the acronym is not first properly introduced. (e.g. Claim 1 Ulip/CRMP).

The disclosure is objected to because of the following informalities: When referring to sequences, the proper sequence identifier is "SEQ ID NO:" not "SEQ ID N°", which is used throughout the specification. (*See* 37 CFR 1.821). Appropriate correction is required.

Typographical errors: Multiple errors in the header for Fig. 11 on page 7; on page 28 "tissu" instead of "tissue". Appropriate correction is required.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claim 6 is objected to because of the following informalities: The claim is written in improper Markush language. The claim recites the conjunctive "and" twice (Spec. p. 76, ll. 24-

5), where in a proper Markush-type claim there should only be a single "and" separating a list of preceding group members from the final group member. Appropriate correction is required.

Claims 29 and 36 are objected to because they are dependent from nonelected claims. Therefore, claims 29 and 36 have not been further examined on the merits for this reason.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

1. **Claims 6-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**

Base claim 6 is drawn to a method of "administering to a patient...a *therapeutically effective amount...*" [emphasis added] of several compounds with the aim to prevent and treat myelin disorders. The claims read on *in vivo* administration of compounds of disparate character, potential mode of delivery and potential effect. Put another way the claim reads on a genus for a therapeutic compound.

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to

drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification does not contain any examples of administering a therapeutic agent *in vivo* to prevent or treat a myelin disorder. There is a single example *in vitro* of administering antibodies to CRMP2 and CRMP5 resulting in reduced Sema3A inhibition of axonal process extention. (Fig. 11D). Even if this single example was presented *in vivo*, it would not be sufficient to obviate a written description rejection. Thus the disclosure is not descriptive of the complete structure of a representative number of species, which the claims encompass, as one of ordinary skill in the art cannot envision all therapeutically effective amounts of all the proposed agents based on the teachings in the specification. In sum it must therefore be considered that the single disclosed species is not a representative number of species sufficient to convince the skilled artisan that applicant is in possession of the claimed genus.

Enablement

2. **Claims 1-16, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

The invention is drawn to a method of both preventing and treating myelin disorders, through modulation of CRMP proteins, more specifically CRMP2 and CRMP5. The invention requires administration to a patient a therapeutically effective amount of a broad range of compounds, including protein, antibodies and nucleic acids.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in scope and breadth. The invention is drawn to a method of preventing or treating disease (i.e. myelin disorders). In addition the claims are drawn to modulating any CRMP protein, and any activity of said protein. Moreover, the method involves administration of a disparate group of therapeutic agents, including some that read on methods of gene therapy (e.g. antisense nucleic acids and nucleic acids encoding CRMP protein), as well as pharmacological administration of proteins and antibodies.

Nature of the invention. The invention involves one of the most complex and poorly developed areas of biology/medicine: neurobiology. In addition the invention is directed toward *in vivo* applications (i.e. treatment of neurological disorders). Furthermore, to the extent that the

invention is drawn to gene therapy, the level of difficulty in implementing the invention is magnified.

State of the art. The invention is directed to a particular area of neurobiology involving oligodendrocytes, which is poorly developed. Oligodendrocytes are myelinating cells of the Central Nervous System (CNS) that ensheath axonal projections, thereby facilitating saltatory conduction. These cells appear as distinct regions in the brain and spinal cord. There is not much known about factors influencing migration and selection of axonal targets for myelination. The role of collapsing response mediator proteins in migration and selection of axonal targets is not well understood. (*See*, Ricard et al. J. Neurosci., 21(18):7203-7214, at 7203 ¶ 1 (2001); *See also*, Cohen et al. J. Neurochem., 85, 1262-78, at 1262, ¶ 1 (2003)).

Indeed the state of the art is only in the nascent stages of development, and "The fact that neurons and oligodendrocytes may respond to similar signals, mediated by Ulip/CRMPs, *opens new fields of investigation* into the role of the neuron/oligodendrocyte interaction in axonal growth...". ([emphasis added; *See* Ricard et al. at 7213, last ¶). The Ulip/CRMP family of proteins are expressed in developing neurons in the brain as shown in rat models. However, different Ulip/CRMP proteins are expressed differentially throughout the central nervous system (as shown in rats), suggesting that each protein may have a specific role in allowing specific neurons to respond to particular axonal guidance. (*See* Wang and Strittmatter. J. Neurosci. 16(19):6197-207, at 6206, col. 2 (1996)). Furthermore, CRMPs are likely involved with different semaphorins and it is possible that several CRMPs mediate different intracellular actions, in selected areas of the nervous system. (*Id.*) Semaphorins are thought to act as a repellent guidance cue for a variety of axons in the developing brain (e.g. inhibiting axonal

outgrowth). It would follow *a priori*, that merely modulating a given CRMP (i.e. CRMP2), which interacts with a given semaphorin (i.e. Sema3A), does not necessarily translate into prevention or treatment of myelin disorders. In sum the state of art of using CRMPs in prevention and treatment of myelin disorders is under developed.

In addition, viz., gene therapy the state of art is also poorly developed. "...there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (Anderson, Nature, 392: 25-30, at 25 (1998)).

Unpredictability of the art. As the state of the art is poorly developed, it would follow that there is a great deal of unpredictability as to whether modulating CRMP proteins *in vivo* would prevent or provide treatment for myelin disorders.

Moreover, with regard to the invention reading on gene therapy, there is a great deal of unpredictability. Gene therapy is still a highly unpredictable art within biology and medicine. For example, nucleic acids encoding therapeutic products may be erroneously inserted, thus disrupting a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, E., Nature, 421: 678 (2003)) (citing occurrence of leukemia due to insertion nucleic acids used in gene therapy into a particular stretch of DNA); (*see also*, Juengst, ET. BMJ, 326:1410-11(2003)) (indicating that gene transfer often has multiple and unpredictable effects on cells).

Amount of guidance provided. Applicant's contention is that modulation *in vivo*, of expression of Ulip/CRMP proteins using several proposed agents, will result in prevention or treatment of myelin disorders. The primary justification for this conclusion is that the proteins are highly expressed in developing neurons (shown in rats) and some members of this protein family play a role in semaphorin inhibition of oligodendrocyte processes. There is actually

nothing in the disclosure to indicate the myelin sheathing is necessarily enhanced or inhibited by the proposed modulation of any Ulip/CRMP protein. Put another way, the guidance provided only invites the skilled artisan to further experimentation, because the Ulip/CRMP family of proteins affect different semaphorins differentially and multiple CRMPs may interact with a specific semaphorin, for example. (*See supra*, Wang and Strittmatter, at 6206, col. 2). Therefore, it would follow that given the amount of guidance provided and the state of the art, *in vitro* results presented would not necessarily translate into implementing the invention *in vivo*. This is reasonable because even if modulation of a single CRMP protein *did* affect a particular semaphorin (e.g. thereby enhancing myelination or axonal outgrowth), it would not be reasonably true that *in vivo* modulation would result in prevention or treatment. Especially, since no *in vivo* guidance or working examples are provided.

The disclosure does provide some generic guidance as to making some of the supposed therapeutic agents (e.g. using the SELEX process to identify aptamers), however, notably, there is no guidance as to using any of the therapeutic agents (e.g. compounds in claim 6), *in vivo*, to effectuate prevention or treatment of a myelin disorder. For example, viz., gene therapy, there is no indication whether the invention can be implemented using transfection vectors or liposome formulations. Alternatively, viz., administration of purified protein, there is no indication as to the path of delivery, dosage levels or the potential for adverse reactions. On whole, the disclosure does not provide guidance for one of ordinary skill in the art to implement the invention.

Number of working examples. The disclosure does not provide any working examples for treatment of a subject. The specification only teaches expression patterns of CRMP2 and

CRMP5 in cells obtained from adult rat brain. Furthermore, the specification teaches an *in vitro* example where rat brain oligodendrocytes were examined with regard to Sema3A effects (i.e. loss of axonal outgrowth; Spec. at 35), whereby addition of anti-CRMP2 and anti-CRMP5 antibodies to the culture reduced Sema3A inhibition of axonal process extension. (Fig. 11D). This single *in vitro* example does not enable one of skill in the art to use the invention given the unpredictability of outcomes when altering gene expression *in vivo*.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working example, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

GERRY LEFFERS
PRIMARY EXAMINER